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ORIGINAL ARTICLE

Weight change in people with type 2 diabetes: secular trends and the impact of alternative antihyperglycaemic drugs

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Aim: This study aimed to describe the pattern of weight change in people with type 2 diabetes (T2DM) over time and when using alternative treatment regimens.

Methods: Data were from routine clinical practice in the UK. The weight trend was determined for each year from 1995 to 2010 for both prevalent and incident cases. Baseline weight was compared to absolute (mean Δ) and relative weights (% Δ) at 6, 12 and 24 months.

Results: Mean, standardized weight, in prevalent cases increased from 83.4 to 92.1 kg for males and from 73.5 to 79.9 kg for females between 1995 and 2010 ($p < 0.0001$). For incident cases, the respective figures were 86.7 to 93.6 kg for males and 76.0 to 80.7 kg ($p < 0.0001$) for females. Between baseline and 6, 12 and 24 months, there were significant changes in weight for the majority of the treatment regimens selected for analysis. The largest weight increase at 12 months was for the patients who were prescribed a combination therapy with insulin and a thiazolidinedione, with a median increase of 4.1 kg (95% CI −0.60 to 8.0, $p < 0.001$). The largest weight decrease at 12 months was for the patients who were prescribed a combination therapy of metformin and exenatide, with a median decrease of −7.0 kg (95% CI −12.0 to −2.0, $p < 0.001$).

Conclusions: There was a continual increase in body weight in people with T2DM over time, and considerable differences in the impact on weight using alternative treatment regimens. At the same time, glycaemic control remained relatively unchanged.

Keywords: antidiabetic drugs, obesity, secular trends, type 2 diabetes, weight change

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Introduction

Type 2 diabetes (T2DM) is a chronic condition characterized by excess micro- and macrovascular morbidity and mortality [1]. Hyperglycaemia is a risk factor for these complications and, therefore, the attainment of near-normal glycaemia is a major therapeutic target for people with the disease [2]. The benefits of sustained glycaemic control have been shown in the United Kingdom Prospective Diabetes Study, which found that a 0.9% decrease in haemoglobin A1c (HbA1c) in the intensive treatment group, was associated with a 25% reduction in microvascular complications when compared with conventional treatment [3].

Where lifestyle modification has failed to result in appropriate glycaemic control, metformin is now universally recommended as the first-line treatment for patients with T2DM. However, therapy failure occurs within 3 years in over 40% of patients on metformin alone [4], resulting in the need for multiple oral antidiabetes agents (OADs) and, eventually, insulin.

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Pharmacotherapy aiming at normal glycaemia may be associated with an increased risk of hypoglycaemia and weight gain. Increasing weight is of particular concern because more than 80% of the T2DM population are overweight or obese at diagnosis [5], set against a background of increasing obesity in the general population [6,7]. For people with diabetes, obesity may not only increase cardiovascular risk but may also have a detrimental impact on health-related quality of life, treatment adherence and treatment cost-effectiveness [8,9]. Many glucose-lowering therapies, including insulin, sulphonylurea and the thiazolidinediones [(TZDs), or glitazones], are associated with weight gain [8–11]. Conversely, metformin and the newer, incretin-mimetic therapies—the GLP-1 analogues (exenatide and liraglutide) [12] and the dipeptidyl peptidase (DPP)-4 inhibitors (sitagliptin, vildagliptin and saxagliptin) [13]—are associated with weight loss or weight neutrality, which may translate into improved outcomes [9,14].

In this study, we aimed to characterize the secular weight pattern for people with T2DM and, in particular, to evaluate weight change associated with different diabetes treatment regimens, using data from routine clinical practice. In order to place these data in the context of corresponding clinical outcome, we also characterized the pattern of glucose control (HbA1c) in relation to body weight changes as a

function of different glucose-lowering therapeutic regimens. For completeness, we also include reference weight data from the non-diabetic population.

Methods

Ethics Statement

The General Practice Research Database Group has obtained ethical approval from a multicentre research ethics committee for all observational research that does not involve patient involvement. Approval for this particular study was awarded by its Independent Scientific Advisory Committee, reference 11_004.

Data Source

Data were extracted from the General Practice Research Database (GPRD) [15], a longitudinal, anonymized data set derived from over 350 primary care practices in the UK. It contains records for approximately 10 million patients, of whom approximately 5 million are actively registered. Available data include patient demographics, medical history, test results and prescriptions. Ethnicity is not recorded for individual patients and is therefore not included in our study. Diagnostic information in GPRD is recorded using the Read Code classification.

Patient Selection and Coding of Diabetes Type

All patients included in the cohort were registered with a general practice contributing to the GPRD dataset. Patients were extracted with a Read Code indicative of diabetes. As not all Read Codes for diabetes differentiate between type 1 and type 2, and some patient histories may erroneously contain codes for both types, patients with T2DM were defined by one or more of the following:

1. Read Codes exclusively indicative of T2DM
2. Prescription of two classes of OAD
3. A Read Code indicative of T2DM (regardless of others indicative of type 1 or non-specific diabetes) and a prescription for an OAD

Patients were defined as incident cases if they had a minimum of 180 days between registration at the practice and their presentation with diabetes, defined as the earlier of first diagnosis or first prescription of a diabetes medication.

Baseline Characteristics

Baseline date was defined as that on which the treatment regimen was initiated. Baseline weight was defined as the nearest weight measurement recorded prior to baseline date to a maximum of −180 days. Other baseline characteristics (HbA1c, systolic and diastolic blood pressure, cholesterol, high density lipids, low density lipids and triglycerides) were determined as the value nearest to baseline in the preceding 30 days. If no value was recorded, the nearest value to baseline in the subsequent 30 days was recorded. If again no value was recorded, the nearest value in the year prior to baseline was used.

Secular Trends in Weight

The secular trend of weight was analysed for patients with and without T2DM and plotted for each year from 1995 to 2010, inclusively. The first weight value recorded per patient per year was used. Annual mean weights were standardized by age to the population profile for 2010 and presented by sex. Age- and sex-specific weight profiles were also calculated for 2000 and 2010.

Diabetes-specific Treatment Regimens

Treatments were considered in the following categories: (i) exenatide, (ii) DPP-4 inhibitors, (iii) insulin, (iv) metformin, (v) TZDs, (vi) sulphonylurea and (vii) other OADs.

Patients were defined by treatment cohorts based on the criteria of a minimum duration of 180 days on the same therapy combination and a "wash-in" period of at least 90 days between the patients' registering at the practice and their first relevant prescription.

Outcome Measurement

Weight change was measured from baseline to 6, 12 and 24 months (±90 days) both as an absolute change in kilograms and as percentage change, and compared using the Wilcoxon signed rank test. For specific regimens, a rolling 30-day average weight, indexed to baseline, was presented. We also evaluated the mean HbA1c for a limited number of regimens by year, for the study period.

Results

Secular Trends in Weight

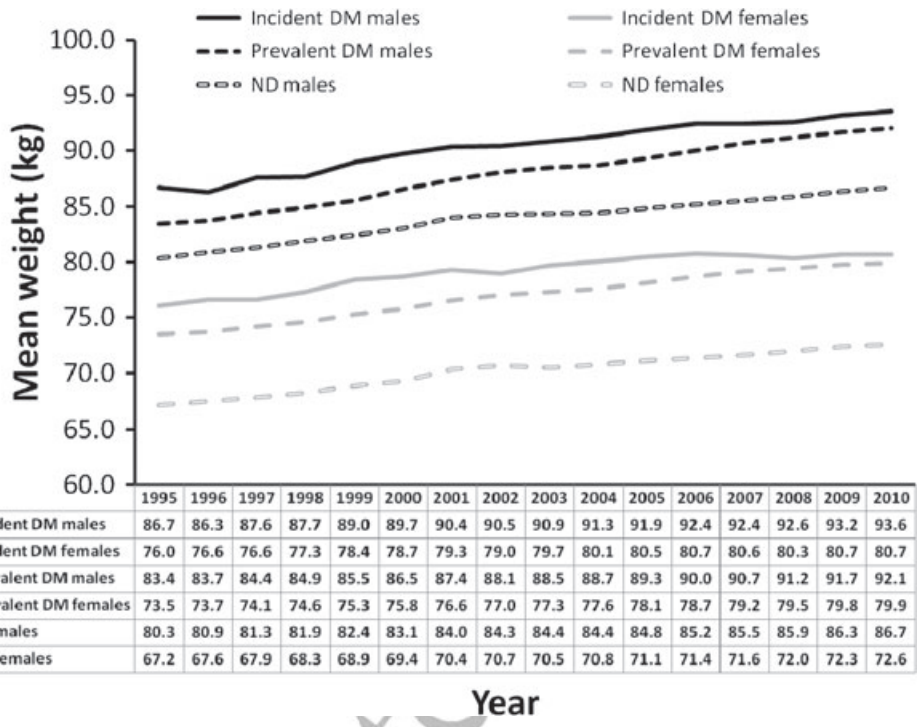
For patients with T2DM, 1 822 790 weight measurements were included in the secular trend analysis, ranging from 38 408 in 1995 to 184 474 in 2010. For the prevalent cohort, mean standardized weight increased from 83.4 to 92.1 kg for males and from 73.5 to 79.9 kg for females (figure 1). For incident cases, the figures were 86.7 to 93.6 kg for males and 76.0 to 80.7 kg for females.

For reference purposes, for the population as a whole aged ≥35 years, corresponding data were available for 4 088 482 people without diabetes. Here, mean standardized weight increased over the study period from 80.3 to 86.7 kg for males and from 67.2 to 72.5 kg for females (figure 1).

Study Subjects and Baseline Characteristics

Baseline characteristics for the T2DM cohorts in 2000 and 2010, presented by 2010 weight quartiles, are shown in Table 1. In both cohorts, mean age was lower in relation to increasing weight, while there was a slight increase in mean HbA1c. Comparison between the cohorts showed an improved profile in 2010 in terms of HbA1c, total cholesterol, lipids and blood pressure.

There were 32 therapy regimens with frequencies greater than 100. The total number of valid therapy periods was 240 307. Of these patients, 149 004 (62.0%), 133 298 (55.5%)



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Incident DM males	86.7	86.3	87.6	87.7	89.0	89.7	90.4	90.5	90.9	91.3	91.9	92.4	92.4	92.6	93.2	93.6
Incident DM females	76.0	76.6	76.6	77.3	78.4	78.7	79.3	79.0	79.7	80.1	80.5	80.7	80.6	80.3	80.7	80.7
Prevalent DM males	83.4	83.7	84.4	84.9	85.5	86.5	87.4	88.1	88.5	88.7	89.3	90.0	90.7	91.2	91.7	92.1
Prevalent DM females	73.5	73.7	74.1	74.6	75.3	75.8	76.6	77.0	77.3	77.6	78.1	78.7	79.2	79.5	79.8	79.9
ND males	80.3	80.9	81.3	81.9	82.4	83.1	84.0	84.3	84.4	84.4	84.8	85.2	85.5	85.9	86.3	86.7
ND females	67.2	67.6	67.9	68.3	68.9	69.4	70.4	70.7	70.5	70.8	71.1	71.4	71.6	72.0	72.3	72.6

Figure 1. Secular trend for age-standardized, mean weight for people with prevalent and incident diabetes and for people without diabetes. DM, diabetes mellitus; ND, non-diabetic.

Table 1. Baseline characteristics by weight quartile of patients with diabetes in 2000 and 2010.

Year	2000				2010			
Weight quartile* (Kg)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
n	21 860	—	19 923	—	16 914	11 495	—	—
Age—years (s.d.)	67.3 (15.2)	64.8 (13.3)	62.1 (12.2)	57.2 (11.9)	69.9 (14.3)	66.9 (12.8)	64.2 (12.1)	59.9 (11.4)
Females—%	67.1	39.8	32.5	28.7	68.1	43.8	33.4	29.3
Systolic BP—mmHg (s.d.)	143.9 (22.6)	145.2 (20.9)	146.0 (20.0)	147.0 (19.4)	134.7 (19.0)	136.2 (17.6)	136.8 (17.0)	138.1 (16.8)
Diastolic BP—mmHg (s.d.)	78.6 (10.6)	80.7 (10.4)	82.7 (10.4)	85.4 (10.5)	74.0 (10.5)	76.0 (10.3)	77.5 (10.3)	79.9 (10.5)
HbA1c—% (s.d.)	7.9 (1.9)	7.9 (1.8)	8.0 (1.8)	8.1 (1.8)	7.2 (1.6)	7.4 (1.6)	7.4 (1.6)	7.6 (1.7)
Total cholesterol—mmol/l (s.d.)	5.4 (1.2)	5.4 (1.1)	5.3 (1.1)	5.3 (1.1)	4.5 (1.1)	4.3 (1.1)	4.3 (1.1)	4.3 (1.1)
HDL—mmol/l (s.d.)	3.2 (1.0)	3.2 (0.9)	3.2 (0.9)	3.1 (0.9)	2.4 (0.9)	2.4 (0.9)	2.4 (0.9)	2.3 (0.9)
LDL—mmol/l (s.d.)	1.4 (0.5)	1.3 (0.4)	1.2 (0.3)	1.1 (0.3)	1.4 (0.4)	1.3 (0.4)	1.2 (0.4)	1.1 (0.3)
Triglycerides—mmol/l (s.d.)	1.9 (1.1)	2.1 (1.2)	2.4 (1.2)	2.6 (1.3)	1.5 (0.8)	1.7 (0.9)	1.8 (1.0)	2.0 (1.0)
GP contacts preceding year—mean n (s.d.)	11.3 (9.7)	11.0 (9.4)	11.1 (9.5)	11.3 (10.2)	15.0 (12.8)	14.3 (12.0)	14.1 (11.7)	14.7 (12.4)

BP, blood pressure; GP, general practice; HbA1c, haemoglobin A1c; s.d., standard deviation.
*Quartiles in 2010—Q1: ≤ 72.0.3 kg; Q2: >; 72.0.3 ≤ 8.10; Q3: > 84.1 ≤ 98.0; Q4: > 98.0.

and 85 925 (35.8%) had weight measurements at circa 180, 365 and 730 days, respectively. The most common regimen was metformin monotherapy with 80 160 observations. Baseline characteristics by regimen are shown in Table 2.

Absolute Weight Change

Absolute changes in weight for the 32 therapy combinations at 6, 12 and 24 months are shown in Table 3. At each time point, there were significant changes in weight for the majority of regimens. For the patients who were prescribed the most common regimen, metformin monotherapy, there was a median average reduction in weight of −1.0 kg [inter-quartile range (IQR) −4.1 to 1.6 kg, $p < 0.001$] at 6 months, −1.1 kg (IQR −4.6 to 2.0 kg, $p < 0.001$) at 12 months and −1.5 kg (IQR −5.0 to 2.0 kg, $p < 0.001$) at 24 months. Insulin monotherapy was associated with an average weight gain of 2.1 kg (IQR −0.9 to 5.9 kg, $p < 0.001$) at 6 months, 3.4 kg (IQR 0.0 to 7.6 kg, $p < 0.001$) at 12 months and 4.5 kg (IQR 0.0 to 9.0 kg, $p < 0.001$) at 24 months.

Table 2. Mean (s.d.) characteristics of patients with type 2 diabetes at baseline by treatment regimen.

Treatment regimen	n	Weight (kg)	Age (years)	Blood pressure systolic + diastolic (mmHg)		HbA1c (%)	Cholesterol (mmol/L)	HLD (mmol/L)	LDL (mmol/L)	Triglycerides (mmol/L)
Met	80 160	90.72 (18.93)	60.46 (12.61)	139.70 (17.98)	80.92 (10.49)	8.41 (1.82)	5.02 (1.25)	1.20 (0.34)	2.79 (0.99)	2.20 (1.18)
Met Sulph	50 696	86.09 (18.41)	62.21 (12.09)	139.92 (18.47)	79.90 (10.21)	8.91 (1.75)	4.74 (1.20)	1.19 (0.35)	2.48 (0.90)	2.15 (1.18)
Sulph	38 611	77.85 (16.43)	66.46 (12.46)	142.20 (20.68)	79.71 (11.12)	8.51 (2.03)	5.12 (1.34)	1.24 (0.38)	2.75 (1.04)	2.12 (1.18)
Ins	13 132	82.00 (18.60)	63.18 (13.28)	138.24 (20.62)	76.64 (11.02)	9.39 (2.10)	4.73 (1.29)	1.22 (0.40)	2.46 (0.93)	2.10 (1.22)
Met TZD	12 937	93.73 (19.44)	58.43 (11.38)	137.67 (16.34)	80.05 (9.66)	8.61 (1.52)	4.56 (1.11)	1.19 (0.33)	2.41 (0.87)	2.19 (1.17)
Met Sulph TZD	10 966	89.64 (19.32)	60.58 (11.20)	137.07 (16.30)	78.28 (9.50)	8.99 (1.44)	4.33 (1.02)	1.17 (0.34)	2.28 (0.77)	2.06 (1.15)
Met Ins	10 337	90.02 (18.66)	59.94 (11.52)	138.33 (17.77)	78.09 (10.16)	9.49 (1.77)	4.56 (1.17)	1.19 (0.36)	2.37 (0.86)	2.16 (1.24)
Sulph TZD	4255	82.17 (17.63)	67.33 (11.53)	140.05 (18.52)	76.95 (10.36)	8.75 (1.63)	4.65 (1.10)	1.22 (0.36)	2.50 (0.88)	2.10 (1.12)
Met Sulph Ins	2758	89.73 (18.70)	60.88 (11.55)	137.02 (17.20)	77.91 (9.87)	9.60 (1.69)	4.36 (1.09)	1.14 (0.33)	2.28 (0.82)	2.14 (1.19)
Met Sulph DPP-4	2282	92.38 (19.58)	61.89 (11.05)	135.10 (15.03)	77.22 (9.22)	8.83 (1.44)	4.08 (0.91)	1.13 (0.33)	2.12 (0.74)	1.98 (1.05)
Met Sulph Other_OAD	1964	87.28 (20.19)	61.98 (11.13)	143.66 (19.02)	80.62 (9.99)	9.27 (1.67)	4.93 (1.22)	1.15 (0.35)	2.47 (1.00)	2.23 (1.21)
Met DPP-4	1933	96.74 (20.68)	58.67 (11.14)	135.11 (15.12)	78.69 (9.54)	8.39 (1.45)	4.31 (1.03)	1.17 (0.37)	2.27 (0.81)	2.06 (1.09)
Met Other_OAD	1469	91.93 (19.87)	58.33 (11.26)	140.22 (17.95)	80.68 (10.42)	8.62 (1.64)	4.84 (1.17)	1.18 (0.34)	2.52 (0.94)	2.28 (1.30)
TZD	1428	86.83 (18.69)	65.31 (11.94)	137.41 (17.57)	76.98 (10.75)	7.64 (1.50)	4.64 (1.11)	1.25 (0.36)	2.56 (0.94)	2.06 (1.06)
Sulph Ins	1383	84.06 (18.65)	68.41 (11.67)	137.27 (19.82)	75.06 (10.85)	9.46 (1.96)	4.43 (1.19)	1.18 (0.39)	2.32 (0.88)	2.17 (1.21)
Sulph Other_OAD	871	80.18 (17.20)	65.75 (11.37)	143.06 (19.59)	79.73 (10.22)	9.06 (2.04)	5.28 (1.34)	1.18 (0.40)	2.66 (0.94)	2.34 (1.33)
Other_OAD	710	83.09 (17.62)	63.21 (13.38)	140.84 (19.10)	80.01 (11.22)	7.99 (1.71)	5.01 (1.27)	1.21 (0.39)	2.66 (0.95)	2.15 (1.17)
Met Sulph Exen	657	110.91 (19.03)	55.78 (10.00)	136.44 (15.71)	79.30 (9.49)	9.25 (1.53)	4.08 (0.94)	1.05 (0.31)	2.10 (0.71)	2.28 (1.20)
Met Ins TZD	535	98.62 (19.89)	56.58 (11.48)	136.32 (16.64)	77.35 (9.85)	9.76 (1.69)	4.42 (1.11)	1.12 (0.30)	2.31 (0.78)	2.33 (1.29)
Met TZD Other_OAD	384	95.37 (22.11)	58.03 (10.88)	137.38 (17.75)	78.66 (9.88)	8.93 (1.52)	4.60 (1.10)	1.23 (0.35)	2.34 (0.80)	2.16 (1.22)
Met Exen	383	112.22 (20.58)	53.14 (10.39)	133.75 (14.64)	79.41 (10.08)	8.49 (1.77)	4.42 (1.10)	1.11 (0.30)	2.35 (0.90)	2.20 (1.15)
Sulph DPP-4	383	86.61 (19.44)	69.04 (11.16)	135.86 (16.21)	74.95 (10.21)	8.66 (1.46)	4.33 (1.08)	1.17 (0.33)	2.34 (0.88)	2.01 (1.09)
Met TZD DPP-4	298	99.72 (21.17)	58.21 (10.78)	134.74 (15.35)	76.99 (9.54)	8.53 (1.42)	4.22 (0.92)	1.18 (0.36)	2.16 (0.72)	2.01 (1.05)
Ins TZD	240	95.96 (17.29)	61.67 (12.24)	137.65 (16.56)	74.94 (10.93)	9.56 (1.93)	4.53 (1.31)	1.12 (0.31)	2.45 (1.03)	2.45 (1.43)
Met Ins Exen	238	109.71 (18.63)	57.05 (9.49)	135.71 (15.91)	76.62 (10.03)	9.46 (1.53)	4.10 (1.08)	1.10 (0.39)	2.11 (0.81)	2.42 (1.30)
Met Ins Other_OAD	237	97.79 (21.91)	58.54 (10.69)	135.89 (17.86)	76.89 (10.22)	9.40 (1.81)	4.43 (1.05)	1.14 (0.29)	2.19 (0.74)	2.31 (1.25)
Met Sulph TZDOther_OAD	215	92.83 (21.12)	61.30 (9.79)	139.50 (16.00)	78.11 (9.45)	9.08 (1.37)	4.46 (1.03)	1.16 (0.31)	2.20 (0.73)	2.11 (1.19)
Met Sulph TZD DPP-4	184	91.68 (19.23)	59.91 (10.93)	134.59 (15.55)	76.34 (9.29)	8.94 (1.40)	4.19 (1.07)	1.18 (0.38)	2.17 (0.83)	1.93 (1.17)
Met Sulph Ins TZD	178	92.90 (20.53)	57.96 (10.97)	135.90 (16.57)	77.92 (10.07)	9.74 (1.62)	4.52 (1.46)	1.17 (0.32)	2.27 (0.78)	2.13 (1.27)
Ins Other_OAD	140	90.96 (19.12)	63.43 (12.74)	138.47 (20.60)	77.45 (10.96)	9.12 (1.69)	4.63 (1.31)	1.21 (0.38)	2.15 (0.83)	2.35 (1.37)
Sulph TZD Other_OAD	128	86.43 (19.30)	67.09 (10.27)	139.86 (16.30)	76.66 (9.26)	9.09 (1.92)	4.63 (1.06)	1.19 (0.33)	2.49 (0.81)	2.19 (1.01)
DPP-4	121	87.34 (20.52)	67.19 (12.30)	135.79 (15.41)	77.73 (9.91)	8.08 (1.53)	4.71 (0.98)	1.25 (0.38)	2.62 (0.88)	2.16 (1.23)

DPP, dipeptidyl peptidase; HbA1c, haemoglobin A1c; OAD, oral antidiabetes agents; s.d., standard deviation; TZD, thiazolidinedione.

Table 3. Absolute and relative mean change in weight from baseline by treatment regimen—in kilograms (% change).

	6 months					12 months					24 months				
Treatment regimen	n	Median	IQR		p	n	Median	IQR		p	n	Median	IQR		p
Met	50 839	−1.00 (−1.34)	−4.08 (−4.70)	1.60 (1.80)	0.000 (0.000)	46 137	−1.10 (−1.39)	−4.60 (−5.17)	2.00 (2.24)	0.000 (0.000)	29 487	−1.50 (−1.64)	−5.00 (−5.77)	2.00 (2.54)	0.000 (0.000)
Met Sulph	30 840	0.50 (0.56)	−2.09 (−2.64)	3.30 (4.00)	0.000 (0.000)	27 950	1.00 (1.03)	−2.00 (−2.60)	4.00 (4.75)	0.000 (0.000)	18 134	1.00 (1.05)	−2.50 (−2.94)	4.50 (5.36)	0.000 (0.000)
Sulph	22 031	1.00 (1.38)	−2.00 (−2.47)	4.10 (5.56)	0.000 (0.000)	20 161	1.50 (1.94)	−1.80 (−2.20)	5.00 (6.43)	0.000 (0.000)	13 715	1.60 (2.11)	−2.00 (−2.42)	5.40 (7.11)	0.000 (0.000)
Met TZD	8482	1.36 (1.45)	−1.50 (−1.69)	4.50 (4.89)	0.000 (0.000)	7723	2.01 (2.48)	−1.00 (−1.28)	5.50 (6.10)	0.000 (0.000)	5198	2.80 (3.03)	−1.00 (−1.07)	6.60 (7.18)	0.000 (0.000)
Insul	7603	2.10 (2.74)	−0.88 (−0.98)	5.90 (7.50)	0.000 (0.000)	6833	3.40 (4.24)	0.00 (0.00)	7.57 (9.68)	0.000 (0.000)	4903	4.50 (5.56)	0.00 (0.00)	9.00 (11.54)	0.000 (0.000)
Met Sulph TZD	7237	1.80 (1.96)	−1.00 (−1.05)	4.60 (5.19)	0.000 (0.000)	6504	2.50 (2.88)	−0.11 (−0.15)	5.90 (6.45)	0.000 (0.000)	4013	3.40 (3.98)	0.00 (0.00)	7.00 (7.87)	0.000 (0.000)
Met Insul	6723	1.00 (1.22)	−1.73 (−1.90)	4.08 (4.82)	0.000 (0.000)	6052	1.80 (1.93)	−1.30 (−1.50)	5.40 (6.13)	0.000 (0.000)	4378	2.40 (2.78)	−1.00 (−1.08)	6.35 (7.39)	0.000 (0.000)
Sulph TZD	2699	2.00 (2.53)	−0.50 (−0.60)	5.00 (6.06)	0.000 (0.000)	2490	3.00 (3.77)	0.00 (0.00)	6.35 (7.79)	0.000 (0.000)	1581	3.73 (4.69)	0.00 (0.00)	7.40 (9.41)	0.000 (0.000)
Met Sulph Insul	1808	1.50 (1.67)	−1.00 (−1.31)	4.59 (5.22)	0.000 (0.000)	1520	2.19 (2.54)	−0.92 (−1.00)	5.50 (6.19)	0.000 (0.000)	858	2.61 (3.04)	−0.70 (−0.71)	6.11 (7.15)	0.000 (0.000)
Met Sulph DPP-4	1555	−0.50 (−0.61)	−2.70 (−2.86)	1.50 (1.64)	0.000 (0.000)	976	−0.90 (−0.90)	−3.10 (−3.53)	1.42 (1.70)	0.000 (0.000)	148	−1.13 (−1.39)	−4.00 (−4.25)	1.73 (2.00)	0.000 (0.001)
Met DPP-4	1304	−1.00 (−1.18)	−3.70 (−3.89)	1.00 (1.17)	0.000 (0.000)	810	−1.12 (−1.46)	−4.50 (−4.55)	1.00 (1.25)	0.000 (0.000)	158	−1.19 (−1.28)	−6.00 (−6.26)	1.00 (1.01)	0.000 (0.000)
Met Sulph Other_OAD	1183	0.00 (0.00)	−3.20 (−3.84)	3.00 (3.51)	0.481 (0.533)	975	0.11 (0.15)	−3.00 (−3.45)	4.54 (5.26)	0.000 (0.000)	614	0.77 (0.90)	−3.00 (−3.58)	6.03 (7.16)	0.000 (0.000)
Met Other_OAD	963	−0.50 (−0.62)	−4.00 (−3.96)	2.90 (3.32)	0.018 (0.035)	778	0.54 (0.58)	−3.00 (−3.45)	4.40 (4.98)	0.011 (0.005)	494	0.90 (0.89)	−3.00 (−3.45)	5.01 (5.99)	0.002 (0.001)
TZD	940	1.80 (1.97)	−1.00 (−1.11)	5.00 (5.88)	0.000 (0.000)	823	2.50 (2.89)	−1.00 (−1.22)	6.00 (6.96)	0.000 (0.000)	530	3.42 (3.81)	−0.63 (−0.93)	7.70 (9.25)	0.000 (0.000)
Sulph Insul	843	2.00 (2.41)	−1.00 (−1.10)	5.00 (6.06)	0.000 (0.000)	704	2.68 (3.04)	−0.80 (−0.93)	5.98 (7.07)	0.000 (0.000)	377	3.20 (3.78)	−0.61 (−0.81)	6.75 (8.48)	0.000 (0.000)
Met Sulph Exen	512	−3.80 (−3.32)	−7.10 (−6.47)	−0.90 (−0.82)	0.000 (0.000)	331	−5.30 (−5.13)	−9.50 (−8.40)	−1.70 (−1.38)	0.000 (0.000)	79	−6.50 (−5.91)	−11.70 (−9.95)	−1.00 (−1.19)	0.000 (0.000)
Sulph Other_OAD	502	0.00 (0.00)	−3.23 (−3.99)	3.00 (3.68)	0.722 (0.815)	409	0.67 (0.94)	−2.73 (−3.30)	4.09 (5.19)	0.009 (0.006)	281	0.90 (1.25)	−3.09 (−4.14)	5.36 (7.02)	0.004 (0.004)
Other_OAD	438	0.00 (0.00)	−3.00 (−3.84)	3.62 (4.51)	0.167 (0.136)	374	0.19 (0.20)	−3.00 (−3.74)	4.00 (4.88)	0.188 (0.116)	247	0.30 (0.32)	−3.18 (−4.22)	4.08 (5.05)	0.319 (0.353)
Met Insul TZD	362	2.39 (2.82)	−1.00 (−0.99)	6.00 (5.66)	0.000 (0.000)	277	4.00 (3.95)	0.00 (0.00)	7.86 (8.15)	0.000 (0.000)	138	4.00 (4.21)	−1.00 (−1.09)	10.00 (10.12)	0.000 (0.000)
Met Exen	304	−4.75 (−4.28)	−8.50 (−7.80)	−1.00 (−1.05)	0.000 (0.000)	171	−6.99 (−6.11)	−12.00 (−10.93)	−2.00 (−1.82)	0.000 (0.000)	39	−8.70 (−7.81)	−12.50 (−11.42)	−2.90 (−2.23)	0.000 (0.000)

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Table 3. Continued.

	6 months					12 months					24 months				
Treatment regimen	n	Median	IQR		p	n	Median	IQR		p	n	Median	IQR		p
Met TZD Other_OAD	247	1.00 (1.19)	−2.00 (−1.92)	4.45 (4.84)	0.000 (0.000)	212	1.60 (1.82)	−1.98 (−1.72)	5.87 (6.24)	0.000 (0.000)	141	2.69 (3.49)	−0.56 (−0.61)	6.23 (6.67)	0.000 (0.000)
Sulph DPP-4	238	0.00 (0.00)	−2.50 (−2.88)	2.00 (2.68)	0.632 (0.782)	154	0.00 (0.00)	−2.50 (−3.24)	2.00 (2.65)	0.588 (0.718)	19	0.70 (0.92)	−4.60 (−7.14)	2.95 (4.19)	0.687 (0.687)
Met TZD DPP-4	194	−0.70 (−0.68)	−3.50 (−3.43)	2.01 (2.24)	0.021 (0.026)	110	−0.43 (−0.46)	−3.05 (−3.15)	3.05 (3.05)	0.695 (0.634)	20	3.20 (4.13)	0.06 (0.07)	6.00 (6.05)	0.010 (0.014)
Met Insul Exen	181	−5.00 (−4.54)	−8.65 (−8.12)	−0.80 (−0.73)	0.000 (0.000)	106	−4.80 (−4.82)	−9.98 (−9.74)	−0.30 (−0.29)	0.000 (0.000)	16	−4.30 (−3.83)	−7.60 (−8.43)	0.00 (0.05)	0.023 (0.026)
Met Insul Other_OAD	173	0.00 (0.00)	−3.30 (−3.44)	3.01 (2.96)	0.595 (0.771)	105	1.00 (1.09)	−2.05 (−2.19)	4.10 (4.91)	0.086 (0.037)	62	3.20 (3.54)	−0.10 (−0.14)	5.70 (7.26)	0.000 (0.000)
Insul TZD	168	2.30 (2.28)	−1.27 (−1.36)	5.43 (6.20)	0.000 (0.000)	123	4.10 (4.37)	−0.60 (−0.73)	8.00 (8.40)	0.000 (0.000)	78	4.77 (5.60)	0.60 (0.66)	9.98 (9.79)	0.000 (0.000)
Met Sulph TZD Other_OAD	141	0.40 (0.58)	−2.39 (−2.71)	3.82 (3.93)	0.113 (0.134)	125	1.00 (1.10)	−1.50 (−2.05)	5.00 (5.03)	0.005 (0.004)	68	2.00 (1.93)	−2.22 (−3.01)	5.29 (6.15)	0.040 (0.039)
Met Sulph Insul TZD	125	2.56 (2.98)	−0.25 (−0.40)	5.95 (6.88)	0.000 (0.000)	87	4.00 (4.62)	−0.20 (−0.27)	7.00 (6.95)	0.000 (0.000)	35	6.00 (6.25)	2.00 (2.44)	9.60 (10.75)	0.000 (0.000)
Met Sulph TZD DPP-4	112	1.00 (1.05)	−1.29 (−1.40)	3.08 (3.81)	0.005 (0.005)	85	1.00 (1.41)	−1.60 (−1.87)	3.70 (4.31)	0.024 (0.022)	22	1.70 (1.78)	−1.66 (−1.64)	3.10 (3.37)	0.322 (0.289)
Insul Other_OAD	98	0.40 (0.42)	−2.78 (−3.03)	4.60 (4.69)	0.123 (0.112)	71	2.30 (2.94)	−1.50 (−2.10)	7.90 (7.81)	0.009 (0.007)	43	5.10 (5.45)	0.70 (1.00)	10.50 (12.86)	0.000 (0.000)
Sulph TZD Other_OAD	80	1.51 (1.60)	−1.48 (−1.68)	4.96 (5.73)	0.006 (0.005)	74	2.50 (3.06)	−0.24 (−0.27)	5.93 (6.82)	0.000 (0.000)	41	2.45 (2.96)	−2.75 (−3.22)	6.61 (8.48)	0.043 (0.030)
DPP-4	79	−0.90 (−0.82)	−3.63 (−4.05)	1.70 (2.41)	0.031 (0.034)	48	−0.63 (−0.78)	−3.95 (−5.13)	1.05 (1.54)	0.043 (0.036)	8	−0.60 (−0.83)	−2.65 (−2.76)	1.75 (2.06)	0.575 (0.674)

DPP, Dipeptidyl peptidase; IQR, inter-quartile range; OAD, oral antidiabetes agents; TZD, thiazolidinedione.

At 6 months, the largest weight increase was associated with the patients who were prescribed a combination therapy of metformin, insulin, sulphonylurea and TZDs, with a median increase of 2.6 kg (IQR −0.25 to 6.0 kg, $p < 0.001$). The largest reduction was for the patients who were prescribed metformin, insulin and exenatide, with a median reduction of −5.0 kg (IQR −8.65 to −0.8 kg, $p < 0.001$).

The largest weight increase at 12 months was for the patients who were prescribed a combination therapy of insulin and TZD, with a median increase of 4.1 kg (IQR −0.60 to 8.0 kg, $p < 0.001$). The largest weight decrease at 12 months was associated with the patients who were prescribed a combination therapy of metformin and exenatide, with a median decrease of −7.0 kg (IQR −12.0 to −2.0 kg, $p < 0.001$).

At 24 months, the largest weight increase was for patients treated with metformin, insulin, sulphonylurea and TZD, with an increase of 6.0 kg (IQR 2.0 to 9.6 kg, $p < 0.001$). The largest decrease was for patients treated with metformin and exenatide: −8.7 kg (IQR −12.5 to −2.9 kg, $p < 0.001$).

Relative Weight Change

Relative weight change is shown in Table 3. In general, these reflected the patterns observed in absolute change. At 6 months the largest weight increase was associated with a combination therapy of metformin, sulphonylurea, insulin and TZD, with an increase of 3.0% (IQR −0.4 to 6.9%, $p < 0.001$). The largest reduction in weight was for metformin, insulin and exenatide, with a reduction of −4.5% (IQR −8.1 to −0.7%, $p < 0.001$).

The largest weight increase at 12 months was for metformin, sulphonylurea, insulin and TZD with an increase of 4.6% (IQR −0.3 to 7.0%, $p < 0.001$). The largest weight decrease at 12 months was associated with a combination therapy of metformin and exenatide, with a decrease of −6.1% (IQR −10.9 to −1.8%, $p < 0.001$).

At 24 months the largest weight increase was for metformin, sulphonylurea, insulin and TZD, with an increase of 6.25% (IQR 2.4 to 10.75%, $p < 0.001$). The largest decrease was for metformin and exenatide: −7.8% (IQR −11.4 to −2.2%, $p < 0.001$).

Rolling Mean Weight by Treatment Regimen

Figure 2 shows the rolling weight average for insulin, metformin and sulphonylurea monotherapies; metformin and sulphonylurea combination therapy; and any combination including DPP-4 inhibitors or exenatide. Both the insulin and sulphonylurea monotherapies and the metformin plus sulphonylurea therapy showed a consistent weight increase from baseline. Metformin monotherapy was associated with an initial gain followed by a decrease. Both the DPP-4 inhibitors and exenatide showed a general downward trend.

Glucose Control—HbA1c

Over the corresponding period, mean HbA1c for patients treated with insulin remained at 8.3%. For metformin, this fell from 7.7 to 7.1%; for metformin and sulphonylurea combined, it fell from 8.3 to 7.6%; and for sulphonylurea, it fell from 7.7 to 7.2%.

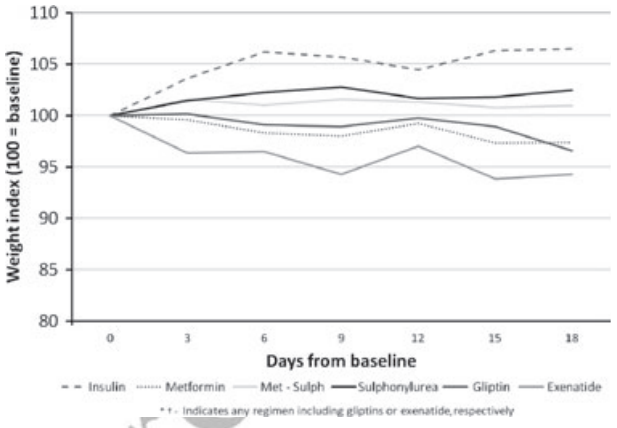

Figure 2. Sixty-day rolling average of weight for specific regimens from baseline to 18 months.

Discussion

There was a continual increase in average weight for all patients and for the subset of patients with T2DM between 1995 and 2010. For those without diabetes, there was an increase in mean weight of 6.3 and 6.4 kg for males and females, respectively. This was greater than the 5.1 and 3.4-kg observed in the Health Survey for England for the same demographic group, but inclusive of those with diabetes [16]. For T2DM, after standardization for age, this increase was approximately 8.6 kg for males and 6.3 kg for females. While we adjusted for age and sex, it is possible that there may be other differences in the cohorts at different time points. For example, the increased emphasis on targeted screening for diabetes has led to the identification of a less morbid population with T2DM [17]. As body mass index is recommended as a filtering variable for screening [18], it is likely that this will be reflected in the profile of newly diagnosed cases. However, the pattern was consistent over time rather than the sudden change that one would expect if screening were influential.

The secular increase in weight may have significant clinical consequences. To place the weight changes evident in this study into context, the average reduction in weight at 2 years using the antiobesity drug orlistat (120 mg) is around 6 kg (3.5 kg vs. placebo) and slightly less at the lower dose [19]. If the health benefits of weight loss claimed for such medications are justifiable, common sense dictates that there must be inverse consequences related to weight gain on diabetes-related drugs. Weight gain in people with T2DM is associated with reduced treatment adherence and health-related quality of life [8,9]. Furthermore, weight gain may further heighten the cardiovascular risk characteristic of T2DM [20]. A recent population-based cohort study has, however, showed a normal life expectancy in subjects with T2DM in primary care when compared to the general population, which may reflect the impact of multiple-risk-factor intervention in people with T2DM [21].

As expected, alternative treatment regimens were associated with differing patterns of weight change, with the greatest increase in weight being associated with the complex and unusual combination therapy of metformin, insulin,

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sulphonylurea and TZD. Weight loss was most pronounced in people treated with metformin plus exenatide, other metformin combinations and regimens including exenatide and the DPP-4 inhibitors. The analysis broadly confirmed clinical trial experience, with regimens involving metformin, exenatide and the DPP-4-inhibitors associated with weight loss, and insulin, sulphonylurea and the TZDs associated with weight gain.

When treatments with different weight properties were used in combination therapy, a modifying effect was observed. For example, while at 24 months, insulin was associated with a median increase of 4.5 kg and metformin with a decrease of 1.5 kg; in combination, there was an overall increase of only 2.4 kg. Consequently, when developing therapeutic strategies for individual patients, the interaction of individual agents with respect to weight should be considered.

There were study limitations. Weight was not collected at precise times and we therefore lost patients who did not have a valid weight measurement within prespecified time frames. Patients who were frequently monitored for weight were therefore more likely to be included in our cohort.

The progressive increase in weight observed in the T2DM cohort may be partly accounted for by the increase in obesity throughout society, in general [6,7]. However, the introduction of evermore stringent glycaemic targets [1] and the implementation of the Quality and Outcomes Framework in the UK in 2004 [22] with its target-driven payment structure, along with clinical trial data advocating intensive glycaemic control [23], may have resulted in increased prescribing of glucose-lowering therapies [22]. Such considerations may contribute to the secular pattern of weight gain seen in this analysis. Furthermore, hypoglycaemia, a recognized consequence of intensified glycaemic control, particularly with sulphonylurea and insulin therapy [24], often results in defensive eating further contributing to weight gain. Indeed, therapeutic approaches resulting in a low risk of hypoglycaemia, such as metformin, DPP-4 inhibitors and exenatide [14], were associated with modest secular downward trends in weight, while the greatest reduction was noted with metformin plus exenatide combination therapy, suggesting that the optimum clinical utility of GLP-1 analogues may be obtained in combination with metformin.

These observations and others [23] raise important questions relating to current therapeutic approaches to managing glycaemia. Treatment costs for T2DM in the UK have almost doubled between 1997 and 2007 [23], largely driven by increased prescription costs. During this period there has been no improvement in overall glycaemic control [23]. The relationship between weight gain and glycaemic control over this period may represent both cause and effect, with increased use of hypoglycaemic therapies contributing to weight gain and weight gain representing a barrier to the improvement of glycaemic control. From the public health perspective, therefore, it may be more pertinent to focus resources not on pharmacotherapy, but on the promotion of lifestyle modification to reduce the incident risk of T2DM and to reduce weight in people with established T2DM. Furthermore, intensification of glycaemic control has not been shown to reduce all-cause mortality in people with T2DM—and may even result in adverse outcomes [25]—and this, coupled with the observations from our analysis, supports the need to develop and implement an individualized therapeutic approach.

Not only is the UK population in general continuously increasing in weight—thus adding to the burden of T2DM—but also those with T2DM are continuously increasing in weight. At a population level, there is depressingly little evidence that any treatment regimen is impacting upon what is conventionally the primary purpose of diabetes-related treatment, that is, glucose control.

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Conflict of Interest

C. Ll. M researched data, contributed to discussion, and wrote and reviewed the manuscript; S. J-J. researched data and edited the manuscript; M. E, A. H. B. and C. D. P. contributed to discussion and reviewed the manuscript; C. J. C contributed to discussion and wrote and reviewed the manuscript.

References

1. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). BMJ 1998; **317**: 703–713.
2. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2009; **32**: 1–11.
3. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352**: 837–853.
4. Brown JB, Conner C, Nichols GA. Secondary failure of metformin monotherapy in clinical practice. Diabetes Care 2010; **33**: 501–506.

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5. Eberhardt MS, Ogden C, Engelgau M, Cadwell B, Hedley AA, Saydah SH. Prevalence of overweight and obesity among adults with diagnosed diabetes—United States, 1988–1994 and 1999–2002. Morb Mortal Wkly Rep 2004; **53**: 1066–1068.
6. Howel D. Trends in the prevalence of obesity and overweight in English adults by age and birth cohort, 1991–2006. Public Health Nutr 2010; **26**: 1–7.
7. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010; **303**: 235–241.
8. Guisasola FÁ, Povedano ST, Krishnarajah G, Lyu R, Mavros P, Yin D. Hypoglycaemic symptoms, treatment satisfaction, adherence and their associations with glycaemic goal in patients with type 2 diabetes mellitus: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) Study. Diabetes Obes Metab 2008; **10**: S25–S32.
9. McEwan P, Evans M, Kan H, Bergenheim K. Understanding the inter-relationship between improved glycaemic control, hypoglycaemia and weight change within a long-term economic model. Diabetes Obes Metab 2010; **12**: 431–436.
10. Heller S. Weight gain during insulin therapy in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2004; **65**: S23–S27.
11. Wright A, Burden ACF, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002; **25**: 330–336.
12. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (Exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005; **28**: 1092–1100.
13. Druckier DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; **368**: 1696–1705.
14. Gilbert MP, Pratley RE. Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus. Am J Med 2009; **122**(Suppl. 6): S11–S12.
15. GPRD Division of the Medicines and Healthcare Products Regulatory Agency. The General Practice Research Database. Available from URL: http://www.gprd.com. Accessed 15 September 2011.
16. The NHS Information Centre. Health Survey for England 2008 Trend Tables. Available from URL: http://www.ic.nhs.uk/pubs/hse08trends. Accessed 12 September 2011.
17. Morgan CL, Peters JR, Currie CJ. The changing prevalence of diagnosed diabetes and its associated vascular complications in a large region of the UK. Diabetic Medicine 2010; **27**: 673–678.
18. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2002; **25**: S5–S20.
19. Rowe R, Cowx M, Poole C, McEwan P, Morgan C, Walker M. The effects of orlistat in patients with diabetes: improvement in glycaemic control and weight loss. Curr Med Res Opin 2005; **21**: 1885–1890.
20. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 2004; **164**: 1422–1426.
21. Lutgers HL, Gerrits EG, Sluiter WJ et al. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (ZODIAC-10). PLoS One 2009; **4**: e6817.
22. Roland M. Linking physicians' pay to the quality of care—a major experiment in the United Kingdom. N Engl J Med 2004; **351**: 1448–1454.
23. Currie CJ, Peters JR, Evans M. Dispensing patterns and financial costs of glucose-lowering therapies in the UK from 2000 to 2008. Diabet Med 2010; **27**: 744–752.
24. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007; **50**: 1140–1147.
25. Currie CJ, Peters JR, Tynan A et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2010; **375**: 481–499.

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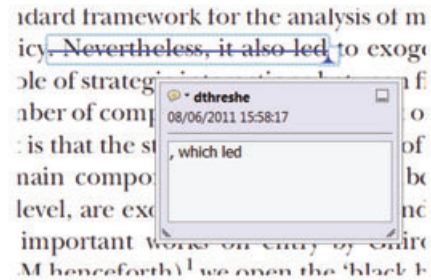
- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

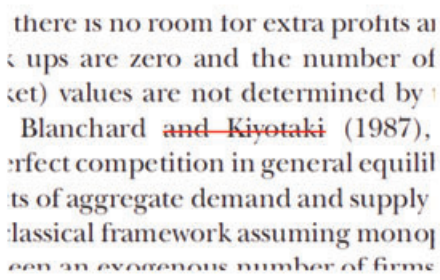


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

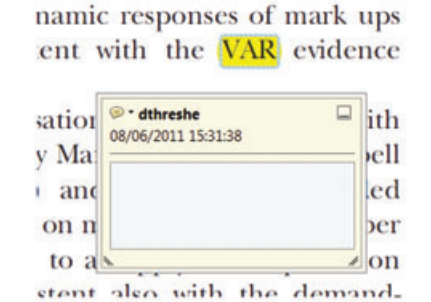


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

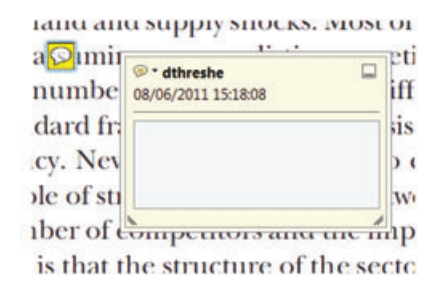


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



WILEY-BLACKWELL

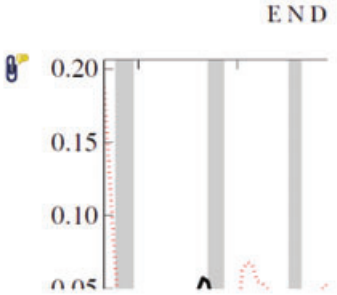
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

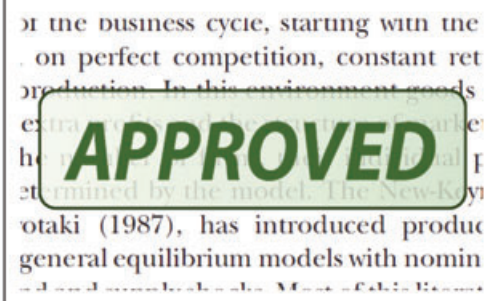


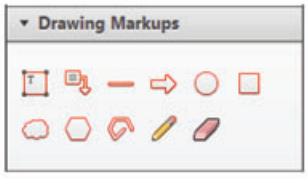
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).



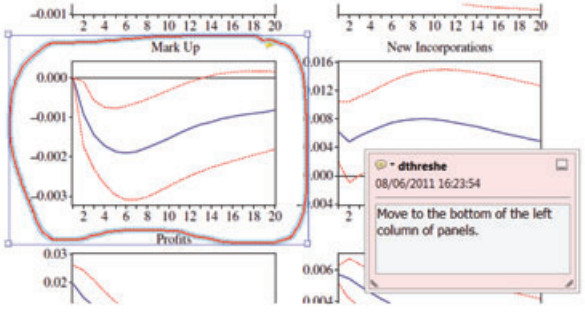


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: